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Stevenage, Hertfordshire SG1 2NY (GB). LOOKER, Brian, Edgar [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(21) International Application Number:
PCT/EP2003/008264

(74) Agent: FLORENCE, Julia, Anne; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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(25) Filing Language: English

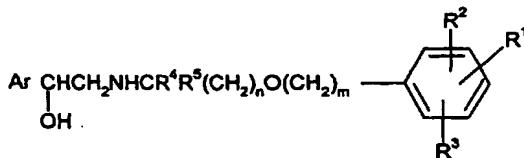
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(26) Publication Language: English

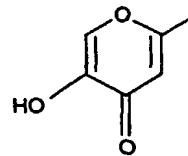
Published:
— with international search report

[Continued on next page]

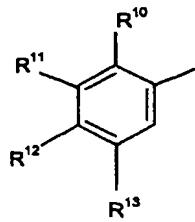
(54) Title: ARYLETHANOLAMINE BETA2-ADRENORECEPTOR AGONIST COMPOUNDS



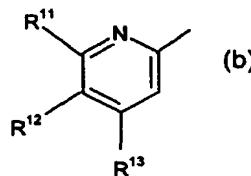
(I)



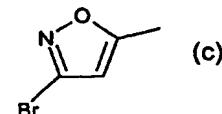
(d)



(a)



(b)



(c)

WO 2004/016578 A3

(57) Abstract: The present invention concerns compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof, wherein: R¹ is hydrogen or -XSO₂NR⁶R⁷; R² and R³ are independently selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, phenyl and C₁₋₆ haloalkyl and Ar is a group selected from and. Processes for preparing said compounds and pharmaceutical formulations containing them are also described. Compounds of formula (I) are useful in the treatment of respiratory diseases



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

10 June 2004

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
GLAXOSMITHKLINE
 Corporate Intell. Property
 Attn. Florence, Julia A.
 (CN925.1)
 980 Great West Road
 Brentford, Middlesex TW8 9GS
 UNITED KINGDOM

Date of mailing (day/month/year) 21/04/2004	
Applicant's or agent's file reference JAF/PG4858	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 03/08264	International filing date (day/month/year) 24/07/2003
Applicant GLAXO GROUP LIMITED	

1. The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chantal Meyer
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Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JAF/PG4858	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/08264	International filing date (day/month/year) 24/07/2003	(Earliest) Priority Date (day/month/year) 25/07/2002
Applicant GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

ARYLETHANOLAMINE BETA2 - ADRENORECEPTOR AGONIST COMPOUNDS

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08264

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07C217/10	C07C311/29	C07C213/00	C07C303/40	C07D215/26
	C07D213/65	C07D265/36	C07D277/68		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/19336 A (IOVIS BIOMEDICAL AND PHARMACEU ; BRON JAN (NL); STERK GEERT JAN (NL);) 20 July 1995 (1995-07-20) claims 1,5-8; examples 1,5-7,9,16 page 15, paragraph 1 – page 16, paragraph 2 -----	1,3,5-7, 12-16
X	EP 0 220 054 A (GLAXO GROUP LTD) 29 April 1987 (1987-04-29) claims 1-3,9,10; examples 16,25 page 4, line 62 – page 5, line 6 -----	1-3,5-8, 12-16
X	EP 0 162 576 A (GLAXO GROUP LTD) 27 November 1985 (1985-11-27) cited in the application claims 1,8,9 page 5, paragraph 3 – page 6, paragraph 3 ----- -/-	1,2,5,8, 12-16

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

2 April 2004

Date of mailing of the international search report

21.04.2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Krische, D

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INTERNATIONAL SEARCH REPORT

Intern	Application No
PCT/EP 03/08264	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 35 24 990 A (GLAXO GROUP LTD) 23 January 1986 (1986-01-23) cited in the application claims 1,15,16; examples 1-13 page 15, line 1 - line 29 page 22, line 25 - line 35 -----	1,12-16
A	GB 2 140 800 A (GLAXO GROUP LTD) 5 December 1984 (1984-12-05) cited in the application claims 1-11; examples 2-4,6-10 page 2, line 62 - page 3, line 15 -----	1,12-16
A	GB 2 230 523 A (GLAXO GROUP LTD) 24 October 1990 (1990-10-24) cited in the application claims 1-6; example 1 page 3, paragraph 2 - paragraph 4 page 6, paragraph 2 - page 8, paragraph 3 -----	1,12-16
A	DE 40 28 398 A (THOMAE GMBH DR K) 12 March 1992 (1992-03-12) claims 1,7,13 -----	16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08264

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

**As a result of the prior review under R. 40.2(e) PCT,
part additional fees are to be refunded.**

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

Continuation of Box I.2

Claims Nos.: -

Present claims 1-16 relate to compounds of formula (I), salts, solvates or "physiologically functional derivatives" thereof. These "derivatives" are defined by reference to a desirable property, namely that they are "physiologically functional".

The claims cover all compounds having this property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I), salts, solvates and as "physiologically functional derivatives" esters thereof.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,3-7,12-15 in part, 2,8-11

Compounds of formula (I) comprising groups Ar a) or b)
useful as beta2-adrenoreceptor agonists and methods and
formulations using these compounds.

2. claims: 1,3-7,12-15 in part

Compounds of formula (I) comprising group Ar c) useful as
beta2-adrenoreceptor agonists and methods and formulations
using these compounds.

3. claims: 1,3-7,12-15 in part

Compounds of formula (I) comprising group Ar d) useful as
beta2-adrenoreceptor agonists and methods and formulations
using these compounds.

4. claim: 16

Alternative processes for the preparation of compounds of
formula (I).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08264

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9519336	A 20-07-1995	AU WO	1533495 A 9519336 A1	01-08-1995 20-07-1995
EP 0220054	A 29-04-1987	CN EP JP US	1048040 A 0220054 A2 62174041 A 4908386 A	26-12-1990 29-04-1987 30-07-1987 13-03-1990
EP 0162576	A 27-11-1985	AT AU AU DE DK EP JP US ZA GB IL NZ PH	44955 T 581887 B2 4134685 A 3571808 D1 173685 A 0162576 A1 60248650 A 4853381 A 8502853 A 2160863 A 75485 A 212367 A 24383 A	15-08-1989 09-03-1989 24-10-1985 31-08-1989 18-10-1985 27-11-1985 09-12-1985 01-08-1989 29-01-1986 02-01-1986 31-10-1988 26-04-1989 13-06-1990
DE 3524990	A 23-01-1986	AU AU BE CH DE DK ES ES FI FR GB GR HU IL IT JP LU NL NO NZ PH PT SE ZA ZA AT CN DE DK EP FI JP JP PT US	582369 B2 4486085 A 902876 A1 665632 A5 3524990 A1 319885 A 8609216 A1 8707925 A1 852755 A 2567510 A1 2162842 A , B 851733 A1 43556 A2 75794 A 1182061 B 61050950 A 86002 A1 8502012 A 852809 A 212726 A 22666 A 80806 A , B 8503466 A 8505297 A 8600193 A 39350 T 86102681 A , B 3566885 D1 13186 A 0178919 A2 860107 A , B, 1785301 C 4074345 B 61148150 A 81819 A , B 4853382 A	23-03-1989 16-01-1986 13-01-1986 31-05-1988 23-01-1986 14-01-1986 16-12-1986 16-11-1987 14-01-1986 17-01-1986 12-02-1986 26-11-1985 30-11-1987 31-01-1989 30-09-1987 13-03-1986 04-08-1986 03-02-1986 14-01-1986 24-02-1989 14-11-1988 01-08-1985 14-01-1986 30-04-1986 29-04-1987 15-01-1989 28-10-1987 26-01-1989 11-07-1987 23-04-1986 11-07-1987 31-08-1993 26-11-1992 05-07-1986 01-02-1986 01-08-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08264

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